Spontaneous adverse drug reaction reporting vs event monitoring: a comparison

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Summary

Spontaneous adverse drug reaction (ADR) reporting is the mainstay of national and international drug safety evaluation in the post-approval phase. A major criticism of the method has been a high, but essentially unquantifiable, level of under-reporting by doctors. A direct comparison has been made between spontaneous ADR reporting and an observational event monitoring system for a group of more than 44 000 patients receiving one or other of a group of seven new drugs. The data suggests that under-reporting by the spontaneous system may be as high as 98% for several clinical events believed to be associated with drug treatment.

Introduction

The occurrence of adverse reactions to drug treatment is a matter of concern to medical practitioners, government regulatory authorities, patients and the pharmaceutical industry. In most developed countries governments sponsor schemes which aim to detect the more serious adverse drug reactions as efficiently as possible and as inexpensively as possible. The two aims may well be mutually incompatible but, rightly or wrongly, virtually all national schemes rely upon spontaneous reporting of suspected drug-related events to a central agency. Those persons entitled to report such events vary from country to country, sometimes being restricted to qualified medical practitioners and sometimes extended to a wide spectrum of health care professionals and the patient.

The strengths and weaknesses of spontaneous ADR reporting have been debated exhaustively[1-3] and general agreement reached that on the positive side such systems potentially cover all patients at all times and are relatively inexpensive to administer. On the negative side there is serious under-reporting and strongly biased perception of what does and what does not constitute an adverse drug reaction.

A major problem has always been that it is extremely difficult to measure the extent of under-reporting and to recognize bias when it occurs. It is the purpose of this paper to present data comparing reporting rates by spontaneous and by event monitoring methods and to examine that data for the existence of bias. The term 'event monitoring' refers to a system of clinical data collection which requires the doctor to report all events whether or not they may be drug-related. All data presented in this paper was collected during the course of several large scale, observational, cohort studies conducted on behalf of six major pharmaceutical companies by the Postmarketing Surveillance Unit of IMS International Ltd.

Methods

The postmarketing surveillance studies from which the present data was taken involved approximately 44 000 patients contributed by approximately 8000 general practitioners who agreed to participate in the studies from all regions of the UK. Data collection from the general practitioner was paper-based and required the completion of simple registration and follow-up forms which were returned to a central unit for coding and analysis. In all cases patients were followed for a period of at least 12 months except for a nonsteroidal anti-inflammatory agent which was monitored for a variable period of time depending upon the duration of treatment. Data collection times were typically at 1, 3, 6, and 12 months after registration into the study. The data items collected included demographic details, diagnosis, drug usage, previous medication, concomitant disease, concomitant medication, specific items of medical history, changes of treatment, consultations, all clinical events, hospitalization and death.

In addition to the event monitoring system general practitioners were provided with a supply of special forms to be used for the spontaneous reporting of events perceived by the doctor to be possibly drug-related. Doctors were reminded of their responsibilities in respect of the national 'Yellow Card' scheme and were asked if a card had been completed.

All studies were conducted in compliance with the 'Quadripartite Guidelines' published by the British Medical Association, Royal College of General Practitioners, Association of the British Pharmaceutical Industry and the Committee on Safety of Medicines[4]. The collection of drug-related clinical data simultaneously by event monitoring and by spontaneous reporting systems by the same doctors involving the same patients over the same periods of time provides a unique opportunity to make a direct comparison of the two systems.

All clinical events, including the original diagnosis, were coded using the ICD 9 classification supplemented by a number of additional special categories. The drugs surveyed were a nonsteroidal anti-inflammatory agent, a beta adrenergic blocking agent, an oral bronchodilator, an alpha-adrenergic blocking agent, an ACE-inhibitor and an H_2-antagonist. A total of approximately 44 000 patients were involved representing about 500 000 patient months of observation.

A selected list of ICD 9 code numbers corresponding to commonly occurring drug-related clinical events was drawn up (Table 1). On each occasion that one of the selected code numbers was reported either as an event monitoring item or as a spontaneous event

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Table 1. ICD 9 code numbers and corresponding clinical events

ICD 9 code	*Clinical event*
307.40	Disorder of sleep
410.00	Myocardial infarct
536.80	Dyspepsia
692.70	Dermatitis/eczema 1*
692.90	Dermatitis/eczema 2†
780.40	Dizziness
780.50	Sleep disturb
781.80	Tremor
782.10	Rash
784.00	Headache
785.00	Tachycardia
785.10	Palpitations
787.00	Nausea/vomiting

*Due to solar radiation; † not due to solar radiation

it was recorded as an occurrence of that specific clinical event. Thus, for example, 'tremor' is coded as 781.8 so it is possible to compare the number of times that 781.8 is reported in the event monitoring system and as a spontaneously reported event giving a measure of the extent of under-reporting in the spontaneous system.

Results

The pattern of clinical events collected by the event monitoring method expressing rates as number of events per 10 000 patients (Table 2) is much as would be expected from established knowledge of the frequency of the selected clinical conditions in association with drug therapy. In the calculation of the totals ICD 9 codes 536.8 and 787 (dyspepsia/nausea/vomiting) for the H_2-antagonist have been subtracted because they are associated with the disease being treated. ICD 9 code 781.8 (tremor) has similarly been subtracted for the bronchodilator because of its specific association and high frequency in the drug concerned.

The pattern of clinical events collected by the spontaneous reporting method, expressed as rates as defined in the last paragraph (Table 3) was somewhat similar but at a greatly lower reporting rate.

A comparison of the absolute numbers of events reported by the two methods (Table 4) shows a remarkably consistent ratio for all of the selected ICD 9 codes with the exception of code number 785 (tachycardia) which was reported spontaneously at about twice the rate of the others. An average spontaneous reporting rate of just over 2% for the selected common events is unexpectedly low, implying under-reporting of about 98%.

Reporting bias is also apparent from the present data. Code numbers 692.7, 692.8 and 782.1 (rash/

Table 2. Number of events per 10 000 patients (absolute numbers)

ICD 9 code	*Drug / Number of patients / Clinical event*	*ART 10 800*	*RES 8807*	*BP1 5021*	*BP2 5622*	*BP3 2556*	*BP4 2716*	*GI 6703*	*RCO 2001*	*Totals 44 226*
307.4	Disorder of sleep	199 (215)	171 (151)	127 (64)	91 (51)	172 (44)	147 (40)	101 (68)	105 (21)	148 (654)
410	Myocardial infarct	66 (71)	124 (109)	171 (86)	98 (55)	121 (31)	85 (23)	52 (35)	40 (8)	95 (418)
536.8	Dyspepsia	696 (752)	351 (310)	398 (200)	249 (140)	348 (89)	213 (58)	1343 (900)	460 (92)	437 (2541)
692.7	Dermatitis/eczema 1	6 (7)	11 (10)	18 (9)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	6 (27)
692.9	Dermatitis/eczema 2	133 (144)	295 (260)	167 (84)	60 (34)	141 (36)	70 (19)	121 (81)	85 (17)	153 (675)
780.4	Dizziness	315 (340)	280 (247)	639 (321)	505 (284)	606 (155)	674 (183)	131 (88)	195 (39)	375 (1657)
780.5	Sleep disturb	31 (34)	44 (39)	50 (25)	32 (18)	55 (14)	37 (10)	1 (1)	30 (6)	33 (288)
781.8	Tremor	4 (4)	747 (658)	2 (1)	30 (17)	59 (15)	55 (15)	1 (1)	10 (2)	11 (696)
782.1	Rash	172 (186)	346 (305)	211 (106)	130 (73)	137 (35)	96 (26)	97 (65)	75 (15)	183 (811)
784	Headache	247 (267)	347 (306)	595 (299)	523 (294)	704 (180)	545 (148)	191 (129)	165 (33)	374 (1655)
785	Tachycardia	6 (7)	47 (41)	14 (7)	30 (17)	74 (19)	107 (29)	1 (1)	5 (1)	28 (122)
785.1	Palpitations	30 (32)	157 (138)	159 (80)	155 (87)	219 (57)	188 (51)	31 (21)	20 (4)	106 (469)
787	Nausea/vomiting	538 (531)	484 (426)	464 (233)	361 (203)	485 (124)	328 (89)	765 (513)	260 (52)	455 (2221)

Table 3. Number of spontaneous reports per 10 000 patients

ICD 9 code	*Drug / Number of patients / Clinical event*	*ART 10 800*	*RES 8807*	*BP1 5021*	*BP2 5622*	*BP3 2556*	*BP4 2716*	*GI 6703*	*Totals 44 226*
307.4	Disorder of sleep	3	1	4	0	8	4	1	2
410	Myocardial infarct	0	1	4	7	4	7	0	2
536.8	Dyspepsia	10	0	8	1	0	0	1	4
692.7	Dermatitis/eczema 1	0	0	0	0	0	0	0	0
692.9	Dermatitis/eczema 2	1	0	1	0	0	0	1	1
780.4	Dizziness	3	8	26	4	8	7	1	7
780.5	Sleep disturbance	0	0	8	0	0	0	0	1
781.8	Tremor	0	19	0	0	0	0	0	4
782.1	Rash	9	2	10	5	0	4	1	5
784	Headache	1	5	20	11	4	29	1	7
785	Tachycardia	0	5	0	1	4	4	0	2
785.1	Palpitations	0	3	6	5	12	4	0	3
787	Nausea/vomiting	3	8	44	5	4	4	1	9

Note: no spontaneous reports were received in respect of drug RCO

Table 4. Spontaneous vs event monitoring (absolute numbers)

ICD 9 code	*Clinical event*	*Spontaneous*	*Event*	*Spontaneous/event (%)*
307.4	Disorder of sleep	10	654	1.53
410.0	Myocardial infarct	10	418	2.39
536.8	Dyspepsia	17	2541	0.67
692.7	Dermatitis/eczema 1	0	27	0.00
692.9	Dermatitis/eczema 2	3	675	0.44
780.4	Dizziness	30	1657	1.81
780.5	Sleep disturbance	4	147	2.72
781.8	Tremor	17	696	2.44
782.1	Rash	22	811	2.71
784.0	Headache	31	1655	1.87
785.0	Tachycardia	7	122	5.74
785.1	Palpitations	13	469	2.77
787.0	Nausea/vomiting	38	2221	1.71

dermatitis/eczema) indicate a 5 to 1 preponderance for drug ART as compared to drug RES when spontaneous reporting is considered whereas event monitoring indicates a reverse situation with a 2 to 1 preponderance when drug RES is compared to drug ART. A similar reversal is also seen for code number 780.4 (dizziness) for the same two drugs and examination of the tables will reveal similar instances.

Discussion

The data presented makes a direct comparison between spontaneous reporting and event monitoring for certain specific selected clinical conditions defined by precise ICD 9 code numbers. The method that has been used has identified the specified clinical events the first time that they have been recorded at follow-up giving an indication of the number of patients who have reported that particular condition. Thus out of the total number of patients registered into the studies, code number 785.1 (palpitations) was recorded for 469 patients and was the subject of a spontaneous ADR report on 13 occasions. The 469 reported occurrences of palpitations could reasonably be attributed in part to the disease itself and in part to the influence of the drug or drugs administered so the low spontaneous reporting level of 2.77% is undoubtedly too pessimistic. However consideration of a well-recognized drug-related event, that otherwise only occurs uncommonly, such as tremor (ICD 9 code 781.8) was recorded for 696 patients and was the subject of 17 spontaneous reports giving a reporting level of 2.44%. In a similar way dermatological conditions which are well-recognized drug-related events (although they undoubtedly occur for other reasons) were spontaneously reported at a level of 1.65%.

This data suggests a very high level of under-reporting which in many circumstances could be as high as 98% even when well-recognized drug-related events are involved. It intuitively seems likely that serious (potentially fatal), rare and/or bizarre spontaneous reports may be less affected by high levels of under-reporting but further investigation is necessary to confirm or refute that hypothesis. It is of anecdotal interest that there were 27 records of ICD 9 code number 692.7 (dermatitis/eczema associated with solar radiation) giving a rate of 6 per 10 000 patients which were detected by event monitoring yet none were spontaneously reported. This is somewhat surprising following the importance of photosensitivity in the adverse reactions identified as being causally related to the administration of benoxaprofen.

The present data indicates that a single spontaneous report of a commonly occurring clinical event implies the existence of 50 more similar events in the total exposed patient population. Although clinical judgement and experience will sometimes help in determining the significance of this conclusion a less subjective evaluation may be achieved by comparing the incidence of a particular event in the target drug with the same event in drugs that would not be expected to have a causal relationship. A consideration of Table 2 shows that some of the clinical events that have been selected for this paper present a very large maximum to minimum difference in incidence from one drug (or patient group) to another, whereas for others the difference is much smaller. For example it can be seen (Table 2) that 785 (tachycardia) occurs 107 times more frequently in association with drug BP4 than it does in drug GI but the incidence of 787 (nausea/vomiting) is only 2.1 times higher in drug ART than it is in drug RCO. This clearly suggests a stronger relationship in the former case than the latter.

It would be reasonable to argue from the figures (Table 3) for the drugs BP4, GI and RCO that the background incidence of 782.1 (rash) may be approximately 100 per 10 000 patients which indicates that an excess of rash occurs in association with drugs ART, RES and BP1 in a ratio of 2 or 3 to 1. Similarly, and even more clearly, the background incidence of 785.1 (palpitations) from drugs ART, GI and RCO might be about 30 per 10 000 patients suggesting a substantial increase in drugs RES, BP1, BP2, BP3 and BP4.

Bias in spontaneous reporting may arise for a number of reasons particularly as a consequence of subjective attitudes in the doctor's perception of what are and what are not drug-related events. From the present data spontaneous reporting would suggest that drug ART (NSAID) was associated with a 5 to 1 excess of dermatological events when compared with drug RES (bronchodilator). This is to be expected in the light of numerous publications linking skin rashes with NSAID treatment. However, when event monitoring data is examined it is found that there is actually a 2 to 1 excess of dermatological events in drug RES as compared to drug ART. In this instance spontaneous reporting would seem to have given a totally misleading impression. It appears that when

the doctor is asked to make a judgement of causality, as is the case for spontaneous reporting, he is highly influenced by current perceptions and prejudices but when he is freed from attributing causality, as in event monitoring, then he reports what he sees.

The 'Yellow Card' system in the UK, 'Pharmacovigilence' in France and most other national schemes rely entirely upon spontaneous reporting for the collection of adverse drug reaction information. This paper highlights the limitations of spontaneous reporting both in respect of low reporting rates and the existence of bias that may give seriously misleading impressions of the frequency of certain clinical events. It is not suggested that spontaneous reporting should be abandoned since it is the only method by which rare and serious drug-related events can be detected but it is suggested that considerable caution be exercised in the interpretation of spontaneous reports on more common clinical events when incidence rates are of importance.

The importance of rare and serious adverse reactions is undeniable but concern with such events should not be allowed to obscure the equal importance of the greatly more common, less serious events that limit the use of otherwise valuable drugs. There are also other, serious and possibly fatal, clinical events, such as myocardial infarction, which occur commonly but are difficult to correlate with drug treatment and which are infrequently reported spontaneously.

It is becoming increasingly clear that no single system can cover all the requirements for the efficient collection of adverse drug reaction data and that a multiplicity of methods is needed. The present paper demonstrates the importance of using different methods of data collection and emphasizes the need to make direct comparisons between methods.

The direct comparison of clinical event data collection by spontaneous reporting and by an event monitoring system which does not require attribution of causality shows a low rate of reporting by the spontaneous system which is also subject to reporting bias which may be due to current perceptions and prejudices on the part of the doctor. Spontaneous reporting systems, which are used by most governmental agencies around the world, are thus subject to serious limitations in the reliability of the data. It is essential that a multiplicity of methods be available for the detection and quantitation of drug-related clinical events and that wherever possible direct comparisons be made before attributing causality.

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